

words of one research group, "adverse effects of oxidative damage induced by disease or drugs."

Cysteine-supplemented mice and guinea pigs have enjoyed significantly extended life spans, and other animals, challenged with various toxins, have, when pre-supplemented with cysteine, survived considerably longer than non-supplemented controls. In one of these studies, 90% of control rats given large doses of acetaldehyde died. But other rats first given a combination of vitamins C and B, along with cysteine, and then exposed to the same dose of acetaldehyde, all survived. Cysteine's protective mechanisms could relate to its own antioxidant properties, its promotion of glutathione (a major antioxidant) or even, it has been hypothesized, to some ability to participate in DNA repair.

There is inconclusive evidence that cysteine could play a positive role in the treatment of osteoarthritis and rheumatoid arthritis.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

L-cysteine supplementation is contraindicated in those hypersensitive to any component of the preparation.

PRECAUTIONS

Because of lack of long-term safety studies, L-cysteine supplementation should be avoided by children, pregnant women and nursing mothers.

Although the incidence of cystine renal stones is low, they do occur. Those who form renal stones, particularly cystine stones, should avoid L-cysteine supplements.

L-cysteine, like other sulfhydryl-containing substances, could produce a false-positive result in the nitroprusside test for ketone bodies used in diabetes.

ADVERSE REACTIONS

With typical doses of 1 to 1.5 grams daily, the most commonly reported side effects have been gastrointestinal, such as nausea. There are rare reports of cystine renal stone formation.

INTERACTIONS

NUTRITIONAL SUPPLEMENTS

Zinc: L-cysteine complexes with zinc and may increase the absorption of zinc.

Vitamin C: Ascorbic acid may inhibit the oxidation of L-cysteine to L-cystine.

OVERDOSAGE

There are no reports of overdosage in those taking L-cysteine supplements. However, large doses of L-cysteine are neuroexcitotoxic in several species. Single injections of L-cysteine (0.6-1.5 g/kg) into 4-day-old pups resulted in

massive damage to cortical neurons, permanent retinal dystrophy, atrophy of the brain and hyperactivity.

DOSAGE AND ADMINISTRATION

The usual supplemental dosage of L-cysteine is 500 milligrams to 1.5 grams daily. Those who supplement with L-cysteine should drink at least six to eight glasses of water daily in order to prevent cystine renal stones. Some studies indicate that an intake of 3 to 5 grams daily of vitamin C may prevent cystine stones. However, high-dose vitamin C itself may contribute to renal stones in some (see Vitamin C).

Another delivery form of L-cysteine is N-acetylcysteine (see N-Acetylcysteine).

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L-Glutamine

DESCRIPTION

L-glutamine is a protein amino acid found in proteins of all life forms. It is classified as a semi-essential or conditionally essential amino acid. This means that under normal circumstances the body can synthesize sufficient L-glutamine to meet physiological demands. However, there are conditions

where the body cannot do so. Recently, L-glutamine has come to be regarded as one of the most important of the amino acids when the body is subjected to such metabolic stress situations as trauma (including surgical trauma), cancer, sepsis and burns. Under such conditions, L-glutamine becomes an essential amino acid, and it is therefore very important to ensure adequate intakes of the amino acid in order to meet the increased physiological demands created by these situations.

L-glutamine is the most abundant amino acid in the body, and plasma glutamine levels are the highest of any amino acid. L-glutamine is predominantly synthesized and stored in skeletal muscle. The amino acid L-glutamate is metabolized to L-glutamine in a reaction catalyzed by the enzyme glutamine synthase, a reaction which, in addition to L-glutamate, requires ammonia, ATP and magnesium.

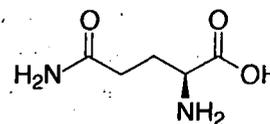
L-glutamine is a very versatile amino acid and participates in many reactions in the body. It is important in the regulation of acid-base balance. L-glutamine allows the kidneys to excrete an acid load, protecting the body against acidosis. This is accomplished by the production of ammonia, which binds hydrogen ions, to produce ammonium cations that are excreted in the urine along with chloride anions. Bicarbonate ions are simultaneously released into the bloodstream. L-glutamine helps protect the body against ammonia toxicity by transporting ammonia, in the form of L-glutamine's amide group, from peripheral tissues to visceral organs, where it can be excreted as ammonium by the kidneys or converted to urea by the liver.

The amide group can also participate in other metabolic activities, as can the amino group of L-glutamine. L-glutamine serves as the most important nitrogen shuttle, supplying nitrogen for metabolic purposes (from glutamine-producing tissues, such as skeletal muscle) to glutamine-consuming tissues.

L-glutamine participates in the formation of purine and pyrimidine nucleotides, amino sugars (such as glucosamine), L-glutamate and other amino acids, nicotinamide adenine dinucleotide and glutathione. It also participates in protein synthesis, energy production and, if necessary, the production of D-glucose and glycogen. Importantly, L-glutamine can serve as the primary respiratory substrate for the production of energy in enterocytes and lymphocytes. L-glutamine is considered an immunonutrient, and supplemental L-glutamine is used in medical foods for such stress situations as trauma, cancer, infections and burns.

The typical dietary intake of L-glutamine is 5 to 10 grams daily. Most dietary L-glutamine comes from animal and plant proteins. Small amounts of free L-glutamine are found in vegetable juices and fermented foods, such as miso and

yogurt. L-glutamine is the amide of L-glutamic acid. Its molecular formula is $C_5H_{10}N_2O_3$, and its molecular weight is 146.15 daltons. The structural formula is:



L-glutamine

L-glutamine is also known as 2-aminoglutaric acid, levoglutamide, (S)-2, 5-diamino-5-oxopentaenoic acid and glutamic acid 5-amide. Its one-letter abbreviation is Q, and it is also abbreviated as Gln. The terms L-glutamine and glutamine are used interchangeably. D-glutamine, the stereoisomer of L-glutamine, does not have, as far as is known, biological activity. L-glutamine is not very soluble in water, and aqueous solutions are unstable at temperatures of 22 to 24 degrees Celsius. For these reasons, the more soluble and more stable glutamine dipeptides are used as delivery forms of L-glutamine in total parenteral nutrition (TPN) solutions. See Glutamine Peptides.

ACTIONS AND PHARMACOLOGY

ACTIONS

Supplemental L-glutamine may have immunomodulatory, anticatabolic/anabolic and gastrointestinal mucosal-protective actions. It may also have antioxidant activity.

MECHANISM OF ACTION

Supplemental L-glutamine's possible immunomodulatory role may be accounted for in a number of ways. L-glutamine appears to play a major role in protecting the integrity of the gastrointestinal tract and, in particular, the large intestine. During catabolic states, the integrity of the intestinal mucosa may be compromised with consequent increased intestinal permeability and translocation of Gram-negative bacteria from the large intestine into the body. The demand for L-glutamine by the intestine, as well as by cells such as lymphocytes, appears to be much greater than that supplied by skeletal muscle, the major storage tissue for L-glutamine. L-glutamine is the preferred respiratory fuel for enterocytes, colonocytes and lymphocytes. Therefore, supplying supplemental L-glutamine under these conditions may do a number of things. For one, it may reverse the catabolic state by sparing skeletal muscle L-glutamine. It also may inhibit translocation of Gram-negative bacteria from the large intestine. L-glutamine helps maintain secretory IgA, which functions primarily by preventing the attachment of bacteria to mucosal cells.

L-glutamine appears to be required to support the proliferation of mitogen-stimulated lymphocytes, as well as the

production of interleukin-2 (IL-2) and interferon-gamma (IFN-gamma). It is also required for the maintenance of lymphokine-activated killer cells (LAK). L-glutamine can enhance phagocytosis by neutrophils and monocytes. It can lead to an increased synthesis of glutathione in the intestine, which may also play a role in maintaining the integrity of the intestinal mucosa by ameliorating oxidative stress.

The exact mechanism of the possible immunomodulatory action of supplemental L-glutamine, however, remains unclear. It is conceivable that the major effect of L-glutamine occurs at the level of the intestine. Perhaps enteral L-glutamine acts directly on intestine-associated lymphoid tissue and stimulates overall immune function by that mechanism, without passing beyond the splanchnic bed.

The anticatabolic/anabolic activity of supplemental L-glutamine can be explained by its effect in sparing skeletal muscle L-glutamine stores.

PHARMACOKINETICS

Following ingestion, L-glutamine is absorbed from the lumen of the small intestine into the enterocytes. Absorption is efficient and occurs by an active transport mechanism. Some metabolism of the amino acid takes place in the enterocytes. L-glutamine that is not metabolized in the enterocytes enters the portal circulation from whence it is transported to the liver, where again some portion of the amino acid is metabolized. L-glutamine not metabolized in the liver enters the systemic circulation, where it is distributed to the various tissues of the body. L-glutamine participates in various metabolic activities, including the formation of L-glutamate catalyzed by the enzyme glutaminase. It also participates in the synthesis of proteins, glutathione, pyrimidine and purine nucleotides and amino sugars. The transport of L-glutamine into cells is via an active process. L-glutamine is eliminated by glomerular filtration and is almost completely reabsorbed by the renal tubules.

INDICATIONS AND USAGE

Glutamine has been shown to be beneficial when administered in the form of glutamine peptides via TPN in some patients with varying forms of catabolic stress, e.g., some cancer, transplantation, intensive-care, surgical and immune-suppressed patients. Benefits from enteral glutamine supplementation are generally less pronounced, but preliminary significant results have been reported with the use of oral glutamine in very-low-birth-weight infants and in some major trauma patients in whom glutamine seems to strengthen immunity, particularly in the gastrointestinal tract. Glutamine may help protect against some of the side effects of cancer chemotherapy and radiotherapy.

There is little concurring evidence that glutamine is an effective ergogenic aid, but there is some suggestion that it might help protect against exercise-induced immune impairment. Some dated research suggesting that glutamine might help curb alcohol craving has not been followed up. Claims that it helps prevent neurodegenerative disorders or that it modulates mood have not been substantiated.

RESEARCH SUMMARY

Several well-designed studies have demonstrated that the addition of glutamine to TPN helps decrease intestinal permeability and mucosal and villous atrophy in the small intestine. Inhibition of intestinal permeability is believed to decrease microbial translocation and thus reduce infective opportunities in the gut. Increased intestinal permeability has been associated with a number of traumas, illnesses and some surgeries.

Studies have shown worthwhile reductions in length of hospital stay attributed to glutamine-supplemented TPN in bone-marrow transplantation patients and in those who had resection for colon or rectal cancer. In another study, mortality was significantly better in intensive-care patients who received TPN supplemented with glutamine than in those whose TPN did not include glutamine.

In addition, glutamine in TPN has been credited with improving nutritional status in some critically ill patients, including cancer patients. And it appears to allow for more aggressive radiotherapy and chemotherapy by protecting against some of the side effects of those treatments.

Enteral glutamine has also demonstrated positive results. In a recent placebo-controlled study, oral glutamine significantly decreased the severity and duration of painful oral mucositis (stomatitis) in autologous bone-marrow transplantation patients. It was similarly helpful in alleviating radiation-induced oral mucositis in a recent randomized pilot trial. Very-low-birth-weight infants orally supplemented with glutamine between days 3 and 30 of life had far less hospital-acquired sepsis than controls (11% versus 30%) and had better tolerance to enteral feedings.

In a placebo-controlled study examining infectious morbidity in multiple trauma patients, oral glutamine was credited with significantly reducing the incidence of pneumonia, sepsis and bacteremia. In another recent randomized study of critically ill patients, supplementation with oral glutamine was said to have significant hospital cost benefits, reducing cost per survivor by 30%.

While claims that glutamine is an effective ergogenic aid are poorly supported, there is some evidence that the substance can help protect against some of the immune impairment that is sometimes seen in exercise "overtraining." Lower resting

levels of plasma glutamine have been observed in some athletes suffering from overtraining syndrome, characterized, in part, by transient immunosuppression. In a few preliminary studies, oral glutamine supplementation appears to improve some measures of immunity and to decrease post-exercise infection. Results are not consistent, however, and more research is needed.

Some dated research suggesting that oral glutamine might help curb alcohol craving has not been followed up. One study demonstrated a significant decrease in voluntary alcohol consumption in rats supplemented with glutamine. A subsequent small, uncontrolled study focused on a group of subjects with extensive history of alcoholism. Considerable improvement was noted. More research is needed.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Supplemental L-glutamine is contraindicated in those hypersensitive to any component of a glutamine-containing product.

PRECAUTIONS

Pregnant women and nursing mothers should avoid supplemental L-glutamine unless prescribed by a physician.

Those with renal or hepatic failure should exercise caution in the use of supplemental L-glutamine.

ADVERSE REACTIONS

Doses of L-glutamine up to 21 grams daily appear to be well tolerated. Reported adverse reactions are mainly gastrointestinal and not common. They include constipation and bloating. There is one older report of two hypomanic patients whose manic symptoms were exacerbated following the use of 2 to 4 grams daily of L-glutamine. The symptoms resolved when the L-glutamine was stopped. These patients were not rechallenged, nor are there any other reports of this nature.

INTERACTIONS

DRUGS

Human growth hormone: Concomitant use of L-glutamine and human growth hormone may enhance nutrient absorption in those with severe short bowel syndrome. L-glutamine has orphan drug status for this indication.

Indomethacin: Concomitant use of L-glutamine and indomethacin may ameliorate increased intestinal permeability caused by indomethacin. The reported dose used for L-glutamine was 21 grams daily taken in divided doses three times a day. Further, misoprostol is reported to have a synergistic effect with this combination in ameliorating intestinal permeability.

Methotrexate: There is one report that methotrexate may decrease the possible effectiveness of supplemental L-glutamine for chemotherapy-induced mucositis. In another report, nine patients with breast cancer were reported to have decreased symptoms of methotrexate-related toxicity when given supplemental L-glutamine at a dose of 0.5 gram/kilogram/day.

Paclitaxel: In one report, L-glutamine at a dose of 10 grams three times daily, given 24 hours after receiving paclitaxel, appeared to prevent the development of myalgia and arthralgia, adverse reactions of paclitaxel.

DOSAGE AND ADMINISTRATION

L-glutamine is available in capsules, tablets and powder form. It is also available in medical foods for oral and enteral nutrition use and in a dipeptide form for parenteral nutrition use. (See Glutamine Peptides.) Typical doses for those with cancer, AIDS, trauma, burns, infections and other stress-related conditions range from 4 to 21 grams daily. Those who take L-glutamine for these indications must be under medical supervision.

Those with chemotherapy- or radiation-induced stomatitis have taken doses of 2 to 4 grams twice daily or 2 grams four times daily. This was done by dissolving a given amount of L-glutamine in water or normal saline — one gram dissolves in 20.8 ml of water at 30 degrees Celsius — and using it as a swish and swallow. Again, this must be performed under medical supervision. Since L-glutamine is unstable in water, fresh solutions should be prepared daily.

Those who use supplemental L-glutamine as a possible ergogenic aid use between 1.5 to 4.5 grams daily, taken between meals.

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L-Histidine

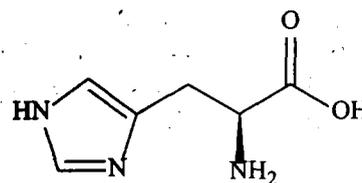
DESCRIPTION

L-histidine is a protein amino acid that is found in the proteins of all life forms. Although most L-histidine is found in proteins, a small amount of free L-histidine does exist in plants and fermented foods. The naturally occurring dipeptides found in muscle, **carosine and anserine are both comprised of L-histidine and beta-alanine.**

L-histidine is one of the 10 essential amino acids for infants.

It has never been clear if L-histidine is an essential amino acid for adults. At the very least, it is a **conditional essential** amino acid for adults. That is, even though L-histidine is synthesized in adult human tissues, sufficient quantities may not be made to meet the physiological requirements imposed by certain stress or disease situations.

L-histidine is a solid water-soluble substance. Chemically, it is called (S)-alpha-amino-1H-imidazole-4-propanoic acid; alpha-amino-4 (or 5)-imidazolepropionic acid; L-2-amino-3-(1H-imidazol-4yl) propionic acid, and glyoxaline-5-alanine. Its IUPAC abbreviation is His, and its one-letter abbreviation is H. L-histidine is classified as a basic amino acid. L-histidine has the following structural formula:



L-Histidine

ACTIONS AND PHARMACOLOGY

ACTIONS

The actions of supplemental L-histidine are entirely unclear. It may have some immunomodulatory as well as antioxidant activity.

MECHANISM OF ACTION

Since the actions of supplemental L-histidine are unclear, any postulated mechanism is entirely speculative. However, some facts are known about L-histidine and some of its metabolites, such as histamine and trans-urocanic acid, which suggest that supplemental L-histidine may one day be